

Position Paper
Association for Patient Oriented Research
Re-engineering the Clinical Research Enterprise
May 19, 2005

The Association for Patient Oriented Research, representing a broad spectrum of physician-scientists devoted to applying the scientific method to improving human health, enthusiastically supports Dr. Elias Zerhouni's plan to re-engineer the clinical research enterprise by way of NIH-supported initiatives to comprehensively integrate the component elements of clinical investigation at academic health centers. Enhancing the scientifically productive interaction between physician-scientists and patients or human volunteers is essential for the success of this important initiative. As a result, all changes should be judged against this goal by asking the following questions.

- **Do they facilitate the scientific productivity of the interactions for the benefit of the public?**
- **Do they encourage physician-scientists (and medically-related doctoral scientists) to select careers in clinical research?**
- **Do they facilitate career development of physician-scientists?**
- **Do they encourage patients and human volunteers to participate in scientific studies?**

The rich tradition of patient-oriented research, based on rigorous observational and experimental science, offers examples of outstanding basic and translational research focused on human disease, and provides models for identifying elements crucial for the success of the new initiatives. The Association is pleased, therefore, to have the opportunity to propose specific goals for the re-engineering program and factors to consider in implementing the program.

1. Goals of Re-engineering

A. Facilitate discovery of new knowledge of human physiology, the pathophysiology of human disease, and the diagnosis, treatment, and prevention of human disease by:

1) Ensuring the availability of crucial infrastructural elements and personnel, including research nursing; information technology, protocol management, and biostatistics (including expert personnel and tools for protocol development, management, monitoring, and auditing, as well as data collection, management, analysis, publication, and presentation); bionutrition; research pharmacy (including compounding of experimental agents); expert personnel to advise in conflict of interest matters; expert personnel to advise on research subject protection; resources and expert personnel to support interactions with the FDA; resources and personnel to ensure compliance with regulations; expert personnel to effect technology transfer (including rapid development of contractual relations with private sector partners); appropriate malpractice and general liability insurance to conduct clinical investigation;

adequately staffed and supported IRBs; and policies and procedures to support inter-institutional collaborations by simplifying cross-institution credentialing and centralization of IRB jurisdictions.

2) Integrating the knowledge and efforts of clinical investigators across the academic medical center and, where appropriate, with other institutions, by mechanisms that optimize the sharing of information, techniques, and reagents, as well as ensuring the most efficient use of personnel and core facilities. In addition, ongoing mechanisms should be provided to help clinical investigators identify the need for additional resources, personnel, administrative structures, or policies to enhance clinical investigation.

3) Providing flexible, outstanding training opportunities to attract new physician investigators that can be tailored to the specific needs and goals of the trainee. Such programs should begin in medical school and build on the principles of adult learning theory, integrating experiential and didactic learning, focusing on information that the trainee believes she or he needs to know, and consolidating the new knowledge by putting it to immediate use. The programs should also reflect trainees' need to advance along their chosen career path as rapidly as possible so that the length of training does not deter outstanding candidates from selecting a career in clinical investigation. Thus, direct participation in ongoing research should be paramount, with the didactic component intimately connected to conducting the research. Advanced degree programs should be available for those seeking comprehensive educational experiences, but should not be required, because some outstanding trainees may feel that the benefits of completing formal degree requirements do not outweigh the impact of such requirements on the length of training or the need to divert attention from intense participation in ongoing research studies. A respect for the diversity of career goals of trainees should guide curricula development so that the course offerings include a range of subjects and the course of study is flexible.

4) Providing outstanding mentoring to trainees and junior faculty members. The mentor occupies the most important position in the training process and thus faculty should be encouraged to act as mentors. In exchange for their commitment, they should be provided with appropriate training, resources, and economic recognition. Methods to assess the quality of mentors and provide constructive feedback are essential.

If institutions choose to create separate departments, institutes, or centers for clinical investigation, it is likely that trainees and faculty members will have appointments in both a traditional department and the new department. Under such circumstances, communication between the trainee's or junior faculty member's mentors in each of the departments (or institutes or centers) must be continuous and precise to ensure that the trainee's or junior faculty member's responsibilities to each mentor and department are clearly defined, and that their aggregate responsibilities to both departments and mentors are appropriate to the training mission.

B. Create credible career ladders leading to scientific independence for trainees demonstrating high achievement. To attract outstanding trainees to a career in clinical investigation it is vital that trainees believe that their careers can

progress in an orderly fashion, culminating in their leading an independent research group.

1) NIH Commitments

a. Grant Support. Since a gap anywhere along the training continuum from medical student to independent faculty member may act as a significant deterrent to choosing a career in clinical investigation, there needs to be a publicly-stated long term commitment to ensure that there are sufficient numbers of funded training positions throughout the path of increasing independence for those demonstrating high achievement. Similarly, there needs to be a commitment to fund a sufficient number of grants for new and established independent investigators. To encourage outstanding mentoring, grants should provide resources to support the time and effort of mentors. In addition, travel funds should be adequate to allow trainees to attend meetings to present their work and to discuss their research with other investigators in their field of interest. Grants should be tailored to recognize the highly collaborative nature of clinical research and the importance of recognizing the contributions of all those participating. Grants supporting the new integrated clinical research program under development should have sufficient resources to achieve the goals outlined in this position paper and have provisions for continued support beyond the current Roadmap period. "The NIH should also review the Medical Science Training Program (MD-PhD) in light of the re-engineering of the clinical research enterprise to assess whether the program can be modified to make a greater contribution to encouraging careers in clinical research." Finally, NIH must ensure that those involved in reviewing clinical research grant proposals have the appropriate experience and expertise.

b. Loan Repayment. Since prolonged training and academic pay scales may act as a deterrent to outstanding individuals choosing careers in clinical investigation, NIH should fund its excellent loan repayment program at levels that potential trainees will recognize as being fair and equitable.

c. National Resources and Standard Setting. The NIH should provide access to national resources, such as those sponsored by NCCR and the individual institutes, to advantage all clinical investigators, including those resources related to genomics, proteomics, imaging, cell culture, and cell therapeutics. Consideration should also be given to also providing access to GMP facilities to prepare novel agents that meet FDA standards for human use. A new "NIH Clinical Investigator Resources" website should be created with links to descriptions of all NIH supported resources for clinical investigators, regardless of the institute or center of origin. NIH should also offer models of excellence for conducting clinical investigation patterned after the procedures used at the NIH Clinical Center and should offer access to software developed by the NIH Clinical Center to expedite protocol development and conduct (see below).

d) Improving and streamlining regulatory procedures. Protecting human subjects and patient/volunteer safety are the highest priorities of the clinical research community. NIH and other appropriate governmental agencies should lead a systematic analysis of the most effective and efficient ways to achieve these goals. Regulatory requirements that do not further these goals should be modified or eliminated.

e) Reconsideration of the restrictions on citizenship on NIH-supported training programs. The rationale underlying this criterion should be reviewed in view of the changing demographics of trainees and the increased international cooperation in conducting clinical research.

2) Institutional and Scientific Community Commitments.

a. Providing excellent clinical facilities and research personnel. Both inpatient and outpatient clinical facilities must be available to support clinical investigation, including resources for confidential discussions related to informed consent, and enhanced resources for specimen collection and preparation. Where appropriate, the facilities also need to address the special needs of normal volunteers, especially those participating in long-term studies. Thus, it cannot be assumed that even high quality clinical facilities designed for patient care automatically meet the needs of clinical investigation. Similarly, institutions must support the training and continuing education of a cadre of research nurses with skills transcending the delivery of patient care. Support for developing national standards for research nursing are required to insure uniform high quality and appropriate expertise. Additional support staff, including research coordinators, data collectors, and protocol monitors and auditors, should be provided to trainees and junior faculty so that they can focus their efforts on the scientific question being addressed.

b. Providing career development support. Institutions should develop programs to encourage medical students to engage in clinical research with a strong scientific component and support the mentors of those programs. They must also provide trainees and junior faculty with adequate space, resources, and time free from clinical, teaching, and administrative responsibilities to allow them to conduct their research. They must also provide outstanding mentoring as described above and credible mechanisms for both assessing the quality of the mentors and making appropriate changes when necessary. Sabbatical leaves should be encouraged, especially those involving basic science laboratories, to ensure the continued scientific growth of faculty members engaged in clinical research. Support for travel to scientific meetings is important for the exchange of scientific information and the opportunity to develop collaborative interactions.

c. Ensuring fair appointments, promotions, and tenure policies. Institutions must demonstrate that their appointments, promotions, and tenure policies recognize the inherent differences in conducting basic and clinical research, especially those involving collaborative efforts. Standards of scientific excellence, however, in both disciplines should be equivalent.

d. Addressing important lifestyle and financial issues. Since many trainees have important family responsibilities in addition to career responsibilities, institutions should have supportive child rearing policies for parents, including both periods of leave time after childbirth or adoption and appropriate modifications in the time to tenure decisions. In addition, opportunities for day care and affordable, nearby housing should be provided.

e. Providing opportunities for dissemination of high quality scholarly activities by clinical investigators. Since clinical studies require much more time to design, execute, and analyze than basic studies, it is important to provide clinical investigators with opportunities to publish high quality, peer-reviewed

scholarship related to their studies before study completion. Thus, existing prestigious journals should be encouraged to expand their publication policy to include papers related to innovative clinical trial design, novel methods to improve the protection of human subjects, creative approaches to data analyses suitable for an increasingly data intensive environment, and other topics related to the conduct of clinical investigation. In addition, consideration should be given to establishing rigorously peer-reviewed new journals devoted to these topics that would allow investigators to demonstrate their scholarship before the completion of their studies.

2. Factors to Consider in Program Implementation

A. General Clinical Research Centers, Comprehensive Cancer Centers, and Clinical Trials Networks all have at least some of the important infrastructural elements identified above. Since these Centers and Networks have undergone rigorous peer-review and have records of effective administration and high productivity, there are important operational advantages in using these Centers and Networks as the initial core of the new program. Thus, building on the strengths of the Centers and Networks is likely to have major benefits with regard to the speed of implementation, confidence about the ability to implement the program as proposed, and the accountability of the program. None of these programs, however, have all of the essential elements described above and thus the new NIH initiative must have sufficient resources to fill the remaining gaps and encourage an integrated approach across departments, centers, and institutes. A broadly representative high level institutional clinical research committee that reports directly to the Dean or similar institutional official should be charged with overseeing the integration of clinical research and developing important infrastructural elements.

B. The centrality of careful observations of patients must be reinforced, and new phenotyping instruments should be developed that can be made available to all investigators. The NIH and others have made major commitments to genomics, proteomics, and systems biology. The value of these investments will be much greater, however, if they can be analyzed in concert with precise clinical descriptions (phenotypes). A human phenome project, in which web-based core templates for databases for diseases under study are prepared using advanced bioinformatics, imaging, and pathologic descriptions and made available through the internet to all clinical investigators would greatly advantage young clinical investigators, providing them with a framework and advanced biostatistical approaches, and allowing them to rapidly test important scientific hypotheses that require genotype-phenotype associations. Such databases and analysis tools would also help establish national phenotyping standards and form the basis of a national meta-database of de-identified information that investigators throughout the U. S. or the world could use for hypothesis development for new studies.

C. The NIH Clinical Center has the expertise, prestige, and resources to establish national models of excellence for clinical investigation. The Clinical Center has made extremely important advances in developing educational programs for clinical investigators (including the production of an outstanding textbook), developing information technology software for protocol development (ProtoType), developing novel patient and staff survey instruments to assess the processes and outcomes of

conducting clinical investigation (Clinical Center Picker Survey), and establishing six standards for conducting clinical investigation, including insightful landmark bioethical standards. Currently, the Clinical Center is exploring new ways to encourage intramural-extramural collaborations. As a result, the Clinical Center should be integrated into the extramural program that evolves, providing its experience and expertise, offering opportunities for 2-way collaborations, and sharing ideas and resources, including software, as appropriate.

D. The Medical Specialty Boards and the ACGME are important stakeholders in improving training in clinical investigation, and their policies and procedures play a crucial role in decisions made by physician-scientist trainees and young faculty members. The impact of current Specialty Board certification and ACGME accreditation policies on trainee career choice in clinical investigation should be studied systematically and the results should form the basis of a respectful dialogue among NIH, Specialty Boards, ACGME, and academic leaders regarding the desirability and feasibility of making adjustments to the policies and procedures of Specialty Boards and the ACGME. Opportunities to streamline residency and fellowship training for individuals choosing careers in clinical investigation should be singled out for especially intense study.

E. The FDA and industry play vital roles in the translational research process. It is important that physician-scientists receive training in understanding the policies and procedures of the FDA. In addition, formal mechanisms for the community of physician-scientists to have a dialogue with the FDA should be established to ensure a two-way flow of important information. It is also important that physician-scientists receive training in interacting constructively with industry, including clear guidelines on conflict of interest. Institutions should provide administrative support to physician-scientists who wish to propose scientific sub-studies to industry-supported clinical trials.

In summary, the Association for Patient-Oriented Research is eager to take a leadership role in supporting the comprehensive approach to re-engineering the clinical research enterprise proposed by Dr. Zerhouni. The individual members of the Association have leadership roles across the entire spectrum of clinical research, and collectively have meaningful expertise and experience in virtually every facet of clinical research. The Association offers to make its expertise available to the NIH as policies and new grant programs are developed. The Association believes that this initiative provides a great opportunity to reorganize and strengthen clinical investigation in a comprehensive and integrated fashion, with the potential for enormous benefits in attracting a new generation of physician-scientists to this noble effort, and dramatically improving both the pace of scientific discovery and the translation of that knowledge into improved health.